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| 10/538,922                     | 06/07/2006  | Philippe Boutin      | Q88618              | 5674             |
| 23373 7590 10/23/2008          |             |                      |                     |                  |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

**Application No.**

10/538,922

**Applicant(s)**

BOUTIN ET AL.

**Examiner**

Stephen Kapushoc

**Art Unit**

1634

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 15 August 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
- 4a) Of the above claim(s) 3, 4 and 6-22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 2 and 5 is/are rejected.
- 7) ☒ Claim(s) 1 and 5 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 13 June 2005 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
- Paper No(s)/Mail Date 06/13/05.
- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### DETAILED ACTION

Claims 1-22 are pending.  
Claims 3, 4, and 6-22 are withdrawn from examination as detailed below.  
Claims 1, 2, and 5 are examined on the merits.

#### *Election/Restrictions*

1. Applicant's election without traverse of the invention of Group 1, claims drawn to methods of diagnosing a predisposition to diabetes comprising analysis of nucleic acid alterations, in the reply filed on 08/15/2008 is acknowledged.

Claims 3, 4, and 6-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 08/15/2008.

#### *Priority*

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 022930853 filed 12/13/2002 with the EPO, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The prior foreign application does not provide any basis for the protective haplotypes, or any SEQ ID NO: 16 or SEQ ID NO: 17, as required by instant claim 5.

### ***Drawings***

5. The drawings are objected to because:

Figure 1 of the drawings indicates a nucleotide number, relative position, and nucleotide content of several polymorphisms in the *gad2* gene. However, while the specification (e.g. p.12-14) indicates that the -1600 position is a G>A polymorphism and the -2004 position is an A>T polymorphism, Figure 1 indicates '-1.6 G>T' and '-2004 G>A'.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

### ***Objection to the Specification***

3. The disclosure is objected to because of the following informalities:

Table 1 of the specification (p.14) contains several typographical errors where it the letter 'G' is replaced with the number '6', the symbol '%' is replaced by '°io', and the number '8' is replaced with the letter 'g'.

Table 2 on p.15 is titled 'fond intake' where the phrase 'food intake' is correct.

Appropriate correction is required.

***Objection to the Specification - Sequence Compliance***

4. This application (10/538,922) contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 at least for the reason(s) set forth below:

In the claims and throughout the specification the application appears to reference sequences from the sequence listing using the terms "SEQ ID No" and "SEQ ID N°". 37 CFR 1.821(d) requires "reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application".

Additionally, Claim 5 references "SEQ ID N° 16 and 17", where the instant sequence listing contains only 15 sequences.

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant must properly identify any sequences from the sequence listing using the identifier "SEQ ID NO:", add the sequences to the Sequence Listing of the instant application, and amend the specification to include the appropriate new SEQ ID NOs

from the sequence listing. If any new sequences are added to the sequence listing Applicants must indicate where in the specification as originally filed such sequences are presented. Alternatively, Applicant may amend the specification to indicate the appropriate SEQ ID NOs or portions of SEQ ID NOs from current Sequence Listing, if the sequences are contained in the current Sequence Listing.

### ***Claim Objections***

5. Claims 1 and 5 are objected to because of the following informalities:

Claim 1 is objected to over recitation of the gene symbol '*gad2*', where upon the first recitation of the symbol in the claims the symbol should be accompanied by a more complete gene name. For example, in claim 1, 'flanking region of the *gad2* (glutamic acid decarboxylase 2) gene'.

Claim 5 is objected to over the specific recitation of non-elected subject matter in the alternative. Applicants have elected for the examination of the claims of group 1, including claims 1, 2, and 5, where claim 5 recites 'the method of one of claim 1 to 4'. Prior to allowance any non-elected subject matter that has not been rejoined will be required to be deleted from the claim.

Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112 2<sup>nd</sup> ¶ - Indefiniteness***

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
8. Claim 5 is unclear over recitation of the phrase 'as depicted in SEQ ID N<sup>o</sup> 16 and 17 respectively', as the phrase appears to reference sequences from the sequence listing, however the instant sequence listing contains only SEQ ID NO: 1-5, and there is no SEQ ID NO: 16 or 17.

***Claim Rejections - 35 USC § 112 1<sup>st</sup> ¶ - Enablement***

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 2, and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

**Nature of the invention and breadth of the claims**

The claims are drawn to methods for diagnosing a predisposition for obesity, and in particular morbid obesity, in a human subject comprising determining whether there is at least one of the alterations -243 A>G, -1.6kb G>A, and -2004 A>T, as recited in claim 1.

The claims further comprise the detection of a protective haplotype including alleles of SNP +61450 C>A and +8397 T>A, as recited in claim 5.

The claims encompass the diagnosis of a predisposition to any type of obesity (e.g. morbid and non-morbid with any BMI) in any population of individuals.

The claims encompass the detection of a wide variety of nucleotide content in the diagnosis of obesity predisposition or detecting a protective haplotype.

The nature of the claimed invention thus requires knowledge of a correlative association between nucleotide content and a predisposition for obesity.

**Direction provided by the specification and working example**

The instant specification teaches an analysis of polymorphic nucleotide content in the *gad2* gene in obese subjects. The specification teaches an analysis of morbidly obese patients (p.13, p.14) and asserts that the -243 G allele, the -1.6kb A allele, and the -2004 T allele are associated with obesity (Table 1). However, it is noted that the data presented in the instant specification does not provide a consistent statistically significant association between the nucleotide content at the -1.6kb and -2004 positions and morbid obesity in the patient populations that were analyzed.

The specification further teaches (p.17) the analysis of haplotype comprising 'alleles of SNP +61450 C>A, and +83897 T>A' and asserts that haplotype of -243, +61450, +83897 ACT is significantly present in non-obese subjects. However, the instant specification does not provide any sequence context that indicates the position or content of the requirements for detecting the +61450 or +83897 SNP positions.

**State of the art, level of skill in the art, and level of unpredictability**

While the state of the art with regard to the detection of variation in any given nucleic acid sequence is high, the unpredictability with regard to the association of any particular variation with a particular phenotype, or the identification of any nucleotide sequence having a particular functionality, is even higher. The unpredictability is demonstrated by the prior art and the instant specification.

Because the claims encompass diagnosing a predisposition to any obesity, while the instant specification provides an analysis only of morbidly obese individuals, it is relevant to point out that Ohshiro et al (2000) teaches that there are genetic distinctions between, for example, mildly obese and morbidly obese individuals. Polymorphisms associated with morbid obesity may not be associated with mild forms of obesity. It is thus unpredictable as to whether or not the asserted associations of the instant specification would be reliably associated with mild forms of obesity where the instant specification provides only an analysis of morbid obesity.

Because the instant claims encompass the analysis of polymorphisms recited as 'alleles of SNP +61450 C>A, and +83897 T>A', but the specification does not provide any limiting structural requirements of the recited polymorphisms, it is relevant to point out the unpredictability in associating any sequence content with a phenotype. For example, Hacker et al (1997) teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (pages 623-627). And because the *gad2* gene has many known polymorphisms (see GeneCard for protein-coding GAD2), including insertion/deletion

polymorphisms, it is not clearly limited as to what sequence elements are required for the +61450 C>A, and +83897 T>A alleles, and thus it is unpredictable as to what sequence content is associated with the asserted protective haplotype.

And while the claims broadly require determining the presence of any form of several claimed biallelic SNPs in the diagnosis of a predisposition to obesity, it is relevant to point out that it is unpredictable if even the particular associations asserted in the specification (i.e. the -243 G allele, the -1.6kb A allele, and the -2004 T allele are associated with obesity) would be robust, reliable, or reproducible in any population. Initially it is relevant to point out that the instant specification does not provide consistent statistically significant associations between the -1.6kb and -2004 alleles and obesity. Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant. Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of  $p=0.05$  would not be considered strong enough for the basis of a conclusion. Furthermore, with regard to the other polymorphic positions disclosed in the specification and recited in the instant claims, the post-filing art indicates a lack of significant association with obesity in several study populations. Swarbick et al (2005) teaches an analysis comprising two different study populations, and fails to find any significant correlations with obesity. Additionally, Hunt et al (2006) fails to find any significant correlation between three SNPs in the *gad2* gene and obesity in a large study population. It is thus highly unpredictable as to whether or not one may

extrapolate the asserted results obtained with the study subjects of the instant application to any other different group of subjects or any other individual subject.

**Quantity of experimentation required**

A larger and prohibitive amount of experimentation would be required to make and use the claimed invention. Such experimentation would require case:control analysis of any study population of interest to establish whether or not any of the broadly encompassed nucleic acid contents of the claims are in fact associated with a predisposition to any form of obesity. Even if such experimentation were to be performed, there is no assurance that any reliable and robust associations would in fact be identified.

**Conclusion**

After consideration of the teaching of the specification and the specific working examples, considering the breadth of the claims, and the unpredictability in the art, it is the conclusion that an undue amount of experimentation would be required to make and use the invention.

***Conclusion***

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should

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/Stephen Kapushoc/  
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